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Comparison of Urea-Based Compounding Moisturizers and Similar Commercial Products on Skin Barrier Function: A Randomized Biometric Study

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Synopsis

Although several commercial moisturizers are available in the market, the continued role of pharmaceutical compounding has been still felt in dry skin management. This study aimed to evaluate the effect of a urea-based compounded moisturizer on barrier function, compared with a similar commercial product. Thirty volunteers with a mean age of 36.15 ± 9.55 years (range 21–56 years) and dry skin were recruited in two groups, one group to apply 5% urea containing hydrophilic petrolatum and the other 10% urea containing hydrophilic petrolatum. In each cohort, the upper parts of right and left forearms were randomly assigned for twice a day application of commercial or compounded products. Whereas the right lower forearm was assigned for application of a cream-based formulation, the left lower one served as the control site and with application of no topical product. Biophysical assessments [transepidermal water loss (TEWL), skin hydration, friction coefficient, pH, and surface lipids], were performed before intervention, at 1 and 4 h after single application, and at 24 h and 1 week twice daily application. In both groups, commercial and compounded moisturizers showed an appropriate and comparable effect on skin barrier function compared with cream-based formulation and no treatment area. However, commercial products led to better improvement in TEWL, 4 h after single application in both groups (p-value = 0.04). In case of 10% urea base formulation, the rate of increase in skin hydration was also significantly higher for a commercial emollient than a compounding product (57.48 ± 11.23 vs. 50.59 ± 11.42, p-value = 0.02). Commercial formulation led to higher acceptability and better improvement in the skin barrier function after single application, probably because of the influence of excipients. The present study did not find sufficient added value for cream-based pharmacy product relative to commercial one and suggests to be replaced in a similar condition.

INTRODUCTION AND BACKGROUND

Pharmacy compounding is defined as customized developing of medical or cosmeceutical preparation for individuals with specific needs (1). Even though many commercial medications and cosmeceuticals are available in the market, which makes medical practice

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more consistent, pharmaceutical compounding still has its role in dermatology. Apparently, market products were unable to resolve all needs of consumers on a personal level and cause some degrees of depersonalization in medical care (2,3).

Dermatology and cosmetology are the most common areas of administration of compounding preparations. Corticosteroids, antibiotics, anti-acne agents, anesthetics, and moisturizers are commonly prescribed topical agents in compounding dermatology (4).

Moisturizers are an important part of dry skin management, which are available in a variety of forms and formulations (5,6). Despite the discovery of novel ingredients for skin care urea is still one of the most useful molecules widely used in compounding and commercial moisturizers. It is a component of the natural moisturizing factor and plays an important role in the maintenance of skin hydration (7).

When it comes to dry skin, many dermatologists tend to use compounded formulations, which let them personalize the concentrations (dosing) and vehicles, according to clinical picture and needs of the patient. Personalizing medications also makes products easier for patients to use, and enhances the treatment compliance (8). However, according to consideration of the Council of Europe, products prepared in pharmacies must offer added value relative to commercialized products (9). Pharmacy preparations are of added value if, due to medical, pharmaceutical, or personal reasons, they are needed by a specific patient or by specific population groups with particular needs (9).

In the current study, we evaluated the effect of two different concentrations (5% and 10%) of urea-based compounded moisturizers on skin barrier function and hydration, compared with similar commercial products we also used.

MATERIAL AND METHOD

STUDY DESIGN AND PARTICIPANTS

It was an intra-subject, double-blinded, randomized, controlled study. Two cohorts of healthy volunteers (men or women), with an age range of 18–60 years, with self-reported and clinically diagnosed dry skin, were recruited after signing written informed consent. Participants with a positive history of major skin diseases, or those using any topical preparations which might influence the skin hydration within past 7 d or used systemic corticosteroids or cytostatic drugs within past 2 weeks, were excluded from the study. Other exclusion criteria were active smoking, presence of any skin diseases on the forearms, and pregnancy or breastfeeding.

The study was performed in compliance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (acceptance code: IR.TUMS.VCR.REC.1398.710). It was also registered in Iranian Register of Clinical Trials with registration code of IRCT20190210042676N9.

TEST PREPARATIONS

We used two commercial water-in-oil products available in the local market (Golafshan Arayesh Cosmetic Laboratory, Tehran, Iran) as follows:

(i) Samin ® emolient cream (urea 5%) Golafshan Co, Tehran, Iran, containing hydrophilic petrolatum (white petrolatum, white wax, stearyl alcohol, and cholesterol), 5% urea, polyacrylamide C13-14 isoparaffin Laureth-7, phenoxyethanol, benzoic acid esters, and deionized water.
(ii) Samin ® emolient cream (urea 10%) Golafshan Co, containing hydrophilic petrolatum (white petrolatum, white wax, stearyl alcohol, and cholesterol), 10% urea, polyacrylamide C13-14 isoparaffin Laureth-7, phenoxyethanol, benzoic acid esters, and deionized water.
(iii) Similar compounded formulations prepared by an expert pharmacist with compounding cream containing hydrophilic petrolatum, urea 5%, and deionized water.
(iv) Compounding cream containing hydrophilic petrolatum, urea 10%, and deionized water.

A simple hydrophilic cream (cream-based preparation) was used as the control formulation, containing cetyl alcohol, stearic acid, propylene glycol, and propyleparaben. The detailed ingredients of the products are shown in Table I.

To prepare the compounding products, urea crystals were triturated to fine powder using mortar and pestle, and then water was added to dissolve urea. Finally, the solution was incorporated into the hydrophilic petrolatum very gradually using a spatula until the smooth and uniform product was obtained. It was performed in room temperature. Condition of preparation was like a pharmacy in which there were no industrial instruments available. The final product was compared with the commercial one by organoleptic properties (color, odor, and texture), and it was similar.

STUDY PROTOCOL

Subjects underwent a conditioning period of 3 d before the study. No application of topical products to the forearms was allowed during this period to ensure there were no residual effects from any product application. Participants were also instructed not to wash the forearms within 3 h of arrival at the test facility.

In the first cohort, upper parts of the right and left forearms were randomly assigned for twice-a-day application of commercial and compounded products containing 5% urea in hydrophilic petrolatum. The same procedure was conducted for commercial and compounded products containing 10% urea in the second cohort of participants. In both cohorts, the right lower forearm was assigned for application of a cream-based formulation and the left lower one served as the control site and application of no topical product.

The study was conducted from March to May 2020. Participants were supposed to use one finger tip of each cream, on a 5-cm × 5-cm area which was assigned for each product.

RANDOMIZATION AND BLINDING

We used a simple randomization sequence using a random number table.

In each cohort, both compounding and industrial preparations as well as cream-based formulation were packaged in similar anonymous jars, distinguished with different codes.

Table I
Moisturizing Products Used in This Study

Test products	Active ingredients	Other ingredients	Water content (%)	pH	Price (IRR)
Industrial urea 5% cream	Hydrophilic petrolatum (white petrolatum, white wax, stearyl alcohol, and cholesterol) and urea	Polyacrylamide C13–14 isoparaffin Laureth-7, phenoxy thanol, benzoic acid esters, and deionized water	61	7.97	362,000
Industrial urea 10% cream				8.04	
Compounded urea 5% cream	Hydrophilic petrolatum (white petrolatum, white wax, stearyl alcohol, and cholesterol) and urea	Deionized water	18.5	9.11	200,000
Compounded urea 10% cream				9.15	
Cream base	Cetyl alcohol, stearic acid, propylene glycol, and propyleparaben		20	6.25	200,000

The site of application of each product was added on the label according to the randomization list by an independent person. The investigator who performed the assessments was unaware of the site of application of each product.

BIOMETRIC ASSESSMENT

Skin biophysical parameters, including transepidermal water loss (TEWL), stratum corneum hydration, friction coefficient, skin surface lipid index, and pH, were measured before intervention, and 1 and 4 h after single application, as well as after 24 h and 1 week of twice-daily applications. Before each measurement, the participants rested in a room with climate control of 22 ± 2°C and relative humidity of 30–40% for 30 min. At the end of the study, the last application was performed at least 12 h before final measurement. All measurements were performed using respective calibrated probes of a TEWAmeter, Corneometer, Frictometer, Sebumeter, and pH meter (MPA 580, Courage & Khazaka electronic GmbH, Cologne, Germany) in controlled room temperature and humidity conditions as previously reported by the authors (10). The skin pH measurement is based on a glass H+ ion sensitive electrode, which is connected to a voltmeter. A drop of deionized water was used to get good contact.

Furthermore, any local adverse events at the site of applications were recorded, and the participants answered a questionnaire regarding tolerability and acceptance of each product on a five-grade Likert scale (5 = extremely satisfied, 4 = very satisfied, 3 = moderately satisfied, 2 = slightly satisfied, and 1 = dissatisfied).

STATISTICAL ANALYSIS

For statistical analysis, we performed descriptive statistics (mean, standard deviation, and percentages). In each time point, statistical differences were tested between four test sites for each parameter, using repeated measure analysis of variance (ANOVA) test. The significance level was set as $p < 0.05$. In case of significance, the post hoc Bonferroni test were performed for pairwise comparison. Statistical significance level was defined as $p < 0.05$.

RESULTS

Thirty participants were enrolled in the study in two cohorts. Each cohort included 15 volunteers (14 women and one man). Mean age and standard deviation in cohorts 1 and 2 were 36.06 ± 9.08 and 35.93 ± 9.03, respectively (range 21–56 years). In each cohort, the baseline data for each parameter compared among four sites using repeated-measure ANOVA test showed no significant difference for any of the evaluated parameters.

COHORT 1 (5% UREA)

Both products significantly increased skin hydration compared with the site of application of the cream-based formulation and no-treatment area in all measurement time points (p-value for ANOVA with repeated measure <0.01). No significant differences were observed between the two products in any of the time points (Figure 1A).

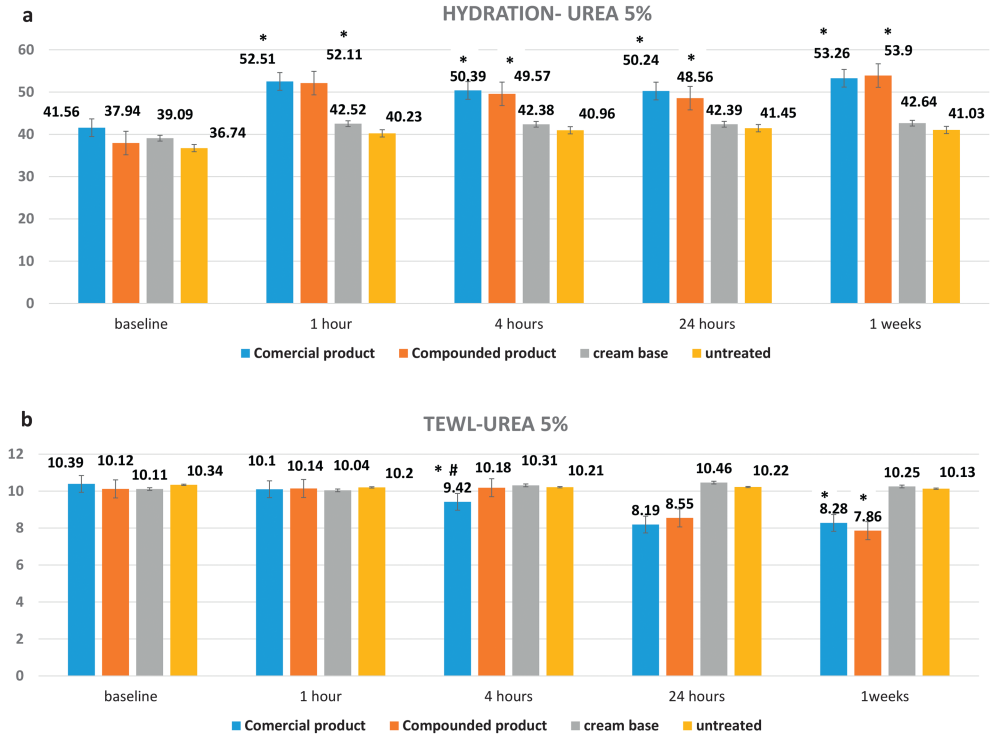

Figure 1. Skin hydration (A) and TEWL (B) for commercial and compounded moisturizers containing urea 5%, after 1, 4, and 24 h as well as 1-week application (*significant compared with cream-based formulation and untreated site, $p < 0.05$) (#significant compared with compounded product $p < 0.05$).

Following a 1-week application, TEWL decreased significantly in sites of application of both products compared with the control site (p-value 0.049 and 0.03 for commercial and compounded product, respectively) (Figure 1B). Four hours after single application, significant decrease occurred in the site of application of commercial moisturizer compared with the control site. This reduction was also significant compared with the site of application of compounded urea-based preparation (9.42 ± 2.01 vs. 10.18 ± 1.65 g/m^2.h, p-value $= 0.04$). No significant differences were detected in TEWL between two products in other time points.

One and 4 h after single application, skin surface lipid content was significantly higher at the site of application of both products than at the untreated area (Table II). No difference was detected in skin serum lipid content between commercial and compounding product in any time point.

We also did not find any significant differences in other skin parameters measured (including skin pH and friction coefficient) between the two products in this cohort using urea 5% (Table II).

COHORT 2 (10% UREA)

In the second group, the improvement in skin water content was also significant compared with the site of application the cream-based formulation and no-treatment area, in all time

Table II
Skin Biophysical Parameters for Commercial and Compounded Moisturizers Containing Urea 5% and Control Sites, after 1, 4, and 24 h as well as 1-Week Application

		Urea 5%				
	Test site	Before	1 h	4 h	24 h	1 week
Sebum (μg/cm^2)	Commercial	1.6 ± 0.54	4.46 ± 0.93	5.93 ± 1.71	3.53 ± 0.88	3.53 ± 0.70
	Compounded	0.8 ± 0.61	7.06 ± 1.24	7.53 ± 2.08	2.66 ± 0.75	2.93 ± 0.79
	Cream base	1.85 ± 1.01	6.93 ± 3.14	3.46 ± 0.87	2.66 ± 0.87	2.13 ± 1.08
	Untreated	1.44 ± 0.95	1.12 ± 0.13	1.61 ± 0.55	1.84 ± 0.552	1.4 ± 0.64
	p-value (compounded vs. commercial)	0.378	0.481	0.556	0.400	0.61
Friction	Commercial	178.39 ± 75.54	449.78 ± 54.038	362.05 ± 172.02	288.76 ± 112.44	437.85 ± 206.33
	Compounded	194.83 ± 94.04	408.63 ± 215.93	407.3 ± 219.27	358.66 ± 160.12	400.66 ± 243.40
	Cream base	295.88 ± 173.01	387.30 ± 164.08	293.40 ± 86.68	310.33 ± 187.45	211.42 ± 35.90
	Untreated	209.96 ± 186.21	177.63 ± 90.71	191.99 ± 116.636	245.02 ± 185.54	258.07 ± 135.66
	p-value (compounded vs. commercial)	0.58	0.69	0. 15	0.369	0.244
pH	Commercial	5.22 ± 0.31	6.32 ± 0.25	6.15 ± 0.23	6.38 ± 0.38	6.26 ± 0.45
	Compounded	5.99 ± 0.51	6.27 ± 0.36	5.97 ± 0.45	6.12 ± 0.31	6 ± 0.31
	Cream base	5.39 ± 0.56	5.65 ± 0.42	5.11 ± 0.40	5.26 ± 0.59	5.55 ± 0.50
	Untreated	5.70 ± 0.42	5.61 ± 0.34	5.57 ± 0.27	5.63 ± 0.41	5.74 ± 0.33
	p-value (compounded vs. commercial)	0.61	0.67	0.52	0.111	0.332

points for both products (p-value for ANOVA with repeated measure <0.01). However, this increase in skin hydration was significantly higher for commercial product 4 h after application (57.48 ± 11.23 vs. 50.59 ± 11.42, p-value = 0.02) (Figure 2A).

Four hours after single application as well as after 1 week of application, the commercial product decreased TEWL significantly comparing with both control sites (p-value < 0.01) (Figure 2B). However, in the case of the compounding product, TEWL reduction was significant compared with the control sites just after the 1-week application.

Four hours after single application, TEWL was also considerably higher in the site of application of the compounded urea product than the commercial one (10.18 ± 1.65 g/m^2.h vs. 9.46 ± 1.03, p-value = 0.04).

A significant increase in the skin pH occurred after 1 week of application of both products, compared with both control sites (p-value < 0.01). In this time point, the skin pH value was considerably higher at the site of application of compounded urea 10% product than commercial preparation; however, it was not statistically significant (p-value = 0.06) (Table III).

Four and 24 h after single application, the skin surface lipid content was significantly higher at the site of compounding urea 10% preparation than the commercial one and untreated area (Table III).

No significant differences were detected in friction coefficient between two groups in any of the measurement time points. However, until 24 h after single application, both products led to significant increase in friction coefficient compared with untreated area.

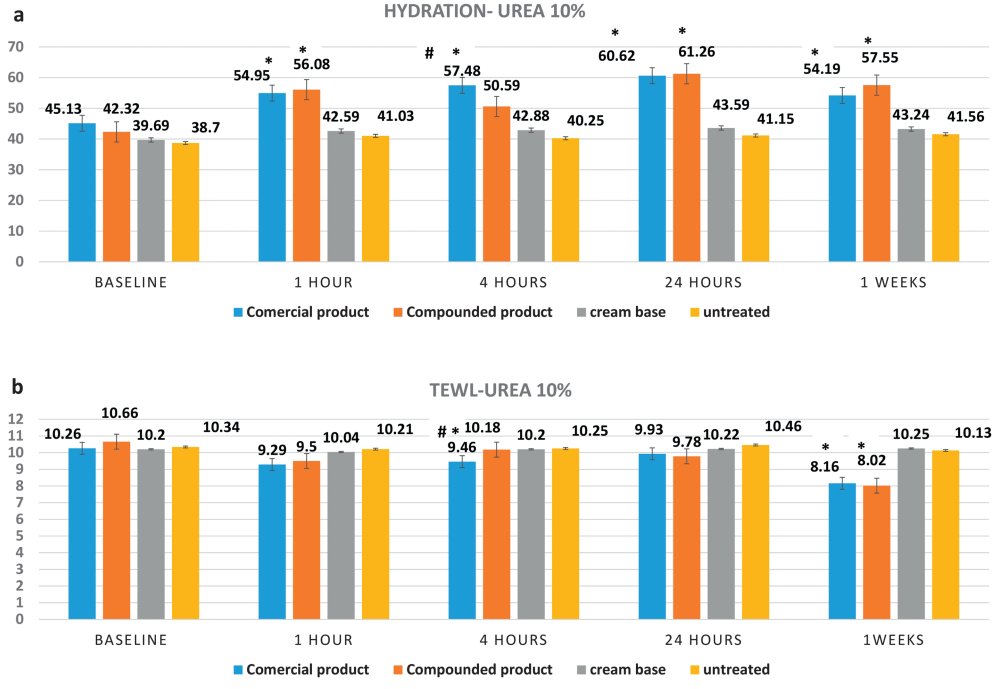

Figure 2. Skin hydration (A) and TEWL (B) for commercial and compounded moisturizers containing urea 10%, after 1, 4, and 24 h as well as 1-week application (*significant compared with cream-based formulation and untreated site, $p < 0.05$) (#significant compared with compounded product, $p < 0.05$).

Table III
Skin Biophysical Parameters for Commercial and Compounded Moisturizers Containing Urea 10% and Control Sites, after 1, 4, and 24 h as well as 1-Week Application

		Urea 10%				
	Test site	Before	1 h	4 h	24 h	1 week
Sebum (μg/cm^2)	Commercial	0.2 ± 0.14	6.86 ± 3.93	2.92 ± 0.62	2.66 ± 0.87	2.66 ± 1.22
	Compounded	0.2 ± 0.141	7.00 ± 1.09	4.86 ± 0.83	4.45 ± 0.88	3.53 ± 0.87
	Cream base	0.45 ± 0.11	6.93 ± 3.14	3.46 ± 0.87	3.45 ± 0.71	2.13 ± 1.08
	Untreated	0.44 ± 0.15	1.16 ± 0.13	1.16 ± 0.55	1.48 ± 0.55	1.4 ± 0.64
	p-value (compounded vs. commercial)	1	0.899	0.049	0.184	0.564
Friction	Commercial	281.22 ± 144.52	594.17 ± 267.97	560.48 ± 293.6	535.12 ± 257.4836	359.38 ± 265.21
	Compounded	238.78 ± 192.80	523.70 ± 278.36	503.74 ± 236.48	513.68 ± 236.48	457.34 ± 217.5
	Cream base	295.88 ± 173.01	208.63 ± 115.93	293.40 ± 86.68	310.33 ± 187.45	211.42 ± 35.90
	Untreated	209.96 ± 186.21	177.63 ± 90.71	191.99 ± 116.636	245.02 ± 185.54	258.07 ± 135.66
	p-value (compounded vs. commercial)	0.374	0.331	0.273	0.820	0.437
pH	Commercial	5.75 ± 0.29	5.98 ± 0.30	5.80 ± 0.24	5.70 ± 0.31	6.04 ± 0.32
	Compounded	5.81 ± 0.39	5.98 ± 0.30	5.85 ± 0.30	5.68 ± 0.29	6.18 ± 0.40
	Cream base	5.39 ± 0.56	5.65 ± 0.42	5.11 ± 0.40	5.26 ± 0.59	5.55 ± 0.50
	Untreated	5.70 ± 0.42	5.61 ± 0.34	5.57 ± 0.27	5.63 ± 0.41	5.74 ± 0.33
	p-value (compounded vs. commercial)	0.263	0.893	0.328	0.593	0.06

No adverse reactions were reported or observed in any of the treatment groups. In both cohorts, participants' satisfaction with treatment was higher for the commercial products (3.85 ± 0.80 vs. 3.66 ± 0.91), and this difference was statistically significant ($p = 0.042$). However, the price of commercial products was slightly higher (Table I).

DISCUSSION

This was a pilot study to investigate the effect of a urea-based compounded moisturizer on barrier function, compared with similar commercial product. The results showed that both moisturizers had appropriate and comparable effects on skin barrier function. However, commercial products led to better improvement in TEWL and skin hydration 4 h after single application.

In both groups, compounded and commercial products were water-in-oil emulsions (appropriate pharmaceutical formulation for xerosis) and contained urea and hydrophilic petrolatum as the main active ingredients.

Urea is a natural endogenous humectant which replaces water in low humidity conditions and maintains a fluidic SC (11,12). Topical formulations with urea concentrations of 5–10%, previously, showed to improve hydration and water retention. In addition, urea can increase the amount of free water in conditions of high humidity (13). In concordance with our findings, improvement in skin hydration using topical urea has been reported within the first hour of application, reaching to the maximum level of 4–6 h following one dose application (14,15).

In addition to moisturizing properties, 10% urea has recently been shown to improve skin barrier function in healthy volunteers associated with the elevated expression of genes involved in SC homeostasis, including the Filaggrin gene-encoding filaggrin protein (16). Concentrations less than 10% have been also shown to strengthen the skin barrier in a series of other studies (17).

Hydrophilic petrolatum is composed of cetyl stearyl alcohol, white Vaseline, and wool wax alcohols (18). High molecular weight hydrocarbons, lanolin alcohols, and acids form an inert layer on the skin, leading to a reduction in TEWL. Thus, occlusion is the most predictable mechanism by which water loss is reduced from the skin.

The results of the current study confirmed the Nasrollahi et al. (19) report, where treatment with a commercial urea 5% hydrophilic petrolatum product resulted in a significant improvement in SC hydration and TEWL in patients with atopic dermatitis.

Despite similar main ingredients, there were some differences in the composition of excipients of two creams, which can be the reason for the slight variation of their effects on skin barrier function. Commercial formulation contained phenoxyethanol, which is a permeation enhancer and promotes permeation of active ingredients by enhancing diffusion or solubility to pass through the SC (20). Usually, this preservative is not used in pharmacies for compounding preparations. In fact, at pharmacies, most compounding products are prepared as preservative free for short time usage.

Polyacrylamide C13–14 isoparaffin Laureth-7 is another excipient used in test commercial products, which is a rheology modifier, stabilizer, thickener, and emulsifier. It could form a polymerized adhesive film on the skin surface which is responsible for the occlusive effect and helps reduce the TEWL (as shown in the current study). A report by Couteau

et al. (21) also confirmed our results, where 5% urea-based formulation containing polyacrylamine C13–14 isoparaffin showed better moisturizing effect than formulation without this excipient.

Lower water content of compounded formulation could be another factor which may affect the moisturizing effect of the product. Kim et al. (22) reported better moistening effect after the application of vehicles containing higher water contents. In the industrial scale, it is preferred to increase the water content of semisolids as an available and inexpensive ingredient to manage their operating margin. Hence, polyacrylamide C13–14 isoparaffin Laureth-7 was used to stabilize the finished product and prevent any phase separation due to high content of water. At pharmacies, more hydrophilic petrolatum and minimum water are used to inhibit any instability.

Dissimilar homogeneity of formulations is another variation factor. Incorporation of ingredients in the compounded product is manual, which may cause uneven spread of ingredients in preparation, leading to insufficient occlusion and increasing the TEWL. In addition, the manufacturing company and pharmacist may provide their ingredients from different sources with dissimilar quality, which may interfere with their therapeutic effects.

Four hours after single application of moisturizers (where participants were not allowed to wash the treated area), the levels of skin surface lipids were relatively higher in the application site of compounded products. This increase was significant in the group using 10% urea cream. It displays that commercial products are less greasy and leave little residue on skin after 4 h. Less oily formulas probably cause superior spreadability and cosmetic acceptability (6), as the present study approved.

Another noteworthy point is the increased skin pH after the 1-week application of both products. It is probably due to high pH of formulations (Table I) because of alkaloid characteristics of urea, affecting skin barrier during repeated applications.

The elevated pH in skin decreases lipid processing in SC, disturbs organization of the lipid bilayers, and increases serine protease activity. The mentioned process affects barrier homeostasis and SC cohesion negatively, and consequently aggravates xerosis condition (23–25).

The formulations differed in pH. A potential reason is that the source of ingredients such as urea and hydrophilic petrolatum could be different in these two types of products. Second, in commercial products, there are benzoic acid esters which reduce the pH of formulation, but this ingredient was not added in compounded products because the pharmacist at pharmacy usually does not add preservative to compounded products. However, Danby et al. (26) reported the same effect of two emollient with pH 4.92 and 7.34 on skin pH because the pH-buffering capacity of skin has been reported to be good.

We describe a methodological approach to compare compounded and commercial moisturizers. Two commonly prescribed formulations containing similar vehicle and active ingredients were used. To decrease the effect of by-products, a simple formulation with limited moisturizing agent and few excipients were selected. The other limitation is the small number of participants and short term of follow-up, despite the fact that the findings were significant. The framework of this study could be applied for comparing more complicated formulations in larger sample sizes to provide better understanding.

CONCLUSION

Although compounded and commercial urea containing hydrophilic petrolatum have demonstrated decent effects on skin barrier function, commercial formulation led to better improvement on skin hydration and TEWL after a single application, probably because of the influence of excipients. Considering this and also the higher acceptability of commercial products, the current study did not come up with a sufficient added value for the pharmacy product relative to commercial one; it is recommended to be replaced in similar conditions.

Disclosure: This study was approved by the Ethics Committee of Tehran University of Medical Sciences (acceptance code: IR.TUMS.VCR.REC.1398.710, date: 2019.12.17). It was also registered in the Iranian Register of Clinical Trials (registration code: IRCT20190210042676N9).

REFERENCES

(1) P. Staubach, S. Salzmann, A. Peveling-Oberhag, V. Weyer, S. Zimmer, G. Gradl, and B. M. Lang, Extemporaneous formulations in Germany-relevance for everyday clinical practice, *J. Dtsch. Dermatol. Ges*, **16**, 567–576 (2018).
(2) J. Gudeman' M. Jozwiakowski, J. Chollet, and M. Randell, Potential risks of pharmacy compounding, *Drugs R.*, **13**(1), 1–8 (2013).
(3) D. L. Elder, A Practical Guide to Contemporary Pharmacy Practice and Compounding, 4th Ed. (Wolters Kluwer Health Press, Philadelphia, PA, 2018)
(4) O. Kiseļova, B. Mauriņa, and V. Šidlovska, Analysis of extemporaneous prescriptions prescribed by dermatovenerologists in Latvia and comparison with standardized compounded preparation monographs of Germany and USA, Medicina (Kaunas), 56(1), 29–33 (2020).
(5) M. Loden, The clinical benefit of moisturizers, *J. Eur. Acad. Dermatol. Venereol.*, **19**(6), 672–688 (2005).
(6) A. Samadi, S. Ahmad Nasrollahi, M. Maghsoudi Ashtiani, C. Abels, and A. Firooz, Changes in skin barrier function following single and repeated applications of 4 types of moisturizers: a randomized controlled trial, *J. Eur. Acad. Dermatol. Venereol.*, **34**(6), e288–e290 (2020).
(7) L. Celleno, Topical urea in skincare: a review, *Dermatol. Ther.*, **31**(6), e12690 (2018).
(8) H. Elliott Campbell, M. Dirk Elston, and C. L. Straughan, A review of the clinical indications, general principles and techniques related to compounding, *J. Am. Acad. Dermatol.*, **83**(1), 179–183 (2020).
(9) M. Sánchez Regañaa, F. Llambí-Mateosb, M. Salleras-Redonneta, M. Iglesias Sanchoa, H. Collgros Totosausa, and P. Umbert Milleta, Compounding as a current therapeutic option in dermatology, *Actas Dermosifiliogr.*, **104**(9), 738–756 (2013).
(10) A. Firooz, H. Zartab, B. Sadr, L. N. Bagherpour, A. Masoudi, F. Fanian, Y. Dowlati, A. H. Ehsani, and A. .Samadi, Daytime changes of skin biophysical characteristics: a study of hydration, transepidermal water loss, pH, sebum, elasticity, erythema, and color index on middle eastern skin, *Indian J. Dermatol.*, **61**(6), 700–708 (2016).
(11) E. H. Mojumdar, Q. D. Pham, D. Topgaard, and E. Sparr, Skin hydration: interplay between molecular dynamics, structure and water uptake in the stratum corneum, *Sci. Rep.*, **7**(1), 15712 (2017).
(12) M. Pan, G. Heinecke, S. Bernardo, C. Tsui, and J. Levitt, Urea: a comprehensive review of the clinical literature, *Dermatol. Online J.*, **19**(11), 20392 (2013).
(13) C. Borelli, S. Bielfeldt, S. Borelli, M. Schaller, and H. C. Korting, Cream or foam in pedal skin care: towards the ideal vehicle for urea used against dry skin, *Int. J. Cosmet. Sci.*, **33**(1), 37–43 (2011).
(14) V. David, Urea creams in skin conditions: composition and outcomes, *Dermatol. Pract.*, **18**(3), 13–15 (2012).
(15) C. Albèr, I. Buraczewska-Norin, V. Kocherbitov, S. Saleem, M. Lodén, and J. Engblom, Effects of water activity and low molecular weight humectants on skin permeability and hydration dynamics - a double-blind, randomized and controlled study, *Int. J. Cosmet. Sci.*, **36**(5), 412–418 (2014).
(16) S. Grether-Beck, I. Felsner, H. Brenden, Z. Kohne, M. Majora, A. Marini, T. Jaenicke, M. Rodriguez-Martin, C. Trullas, M. Hupe, P. M. Elias, and J. Krutmann, Urea uptake enhances barrier function and antimicrobial defense in humans by regulating epidermal gene expression, *J. Invest. Dermatol.*, **132**, 1561–1572 (2012).

(17) S. G. Danby, K. Brown, T. Higgs-Bayliss, J. Chittock, L. Albenali, and M. J. Cork, The effect of an emollient containing urea, ceramide NP, and lactate on skin barrier structure and function in older people with dry skin, *Skin Pharmacol. Physiol.*, **29**, 135–147 (2016).
(18) Y. Anwar and E. J. Lowenstein, Eucerin: a revolutionary formulation still going strong for over a century, *Skinmed*, **14**(6), 437–439 (2016).
(19) S. Ahmad Nasrollahi, A. Ayatollahi, T. Yazdanparast, A. Samadi, H. Hosseini, M. Shamsipour, A. S. Akhlaghi, S. Yadangi, C. Abels, and A. Firooz, Comparison of linoleic acid-containing water-in-oil emulsion with urea-containing water-in-oil emulsion in the treatment of atopic dermatitis: a randomized clinical trial, *Clin. Cosmet. Invest. Dermatol.*, **11**, 21–28 (2018).
(20) R. Chang, A. Raw, R. Lionberger, and L. Yul, Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products, *AAPS J.*, **15**(1), 41–52 (2013).
(21) C. Couteau, L. J. M. Coiffard, and V. Sébille-Rivain, Influence of excipients on moisturizing effect of urea, *Drug Dev. Ind. Pharm.*, **32**(2),239–242 (2006).
(22) H. Kim, J. Ro, S. Barua, D. S. Hwang, S. J. Na, and H. S. Lee, Combined skin moisturization of liposomal serine incorporated in hydrogels prepared with carbopol ETD 2020, rhesperse RM 100 and hyaluronic acid, *Korean J. Physiol. Pharmacol.*, **19**(6), 543–547 (2015).
(23) P. M. Elias, Stratum corneum acidification: how and why? *Exp. Dermatol.*, **24**, 179–180 (2015).
(24) P. M. Elias, The how, why and clinical importance of stratum corneum acidification, *Exp. Dermatol.*, **26**, 999–1003 (2017).
(25) A. Kilic, C. Masur, H. Reich, U. Knie, D. Dähnhardt, S. Dähnhardt-Pfeiffer, and C. Abels, Skin acidification with a water-in-oil emulsion (pH 4) restores disrupted epidermal barrier and improves structure of lipid lamellae in the elderly, *J. Dermatol.*, **46**(6), 457–465 (2019).
(26) S. G. Danby, J. Chalmers, K. Brown, H. C. Williams, and M. J. Cork. A functional mechanistic study of the effect of emollients on the structure and function of the skin barrier, *Br. J. Dermatol.*, **175**(5), 1011–1019 (2016).